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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,922	03/12/2004	Hans Ernst Jan Hofland	020681-001610	6834

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

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08/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,922	HOFLAND ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-41* is/are pending in the application.

4a) Of the above claim(s) *7-10 and 12-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,11 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 5-21-08 is acknowledged.

Claims included in the prosecution are 1, 6, 11 and 38-41.

In view of the amendments, the previous 102 rejections have been withdrawn.

Claim Rejections - 35 USC § 112

1. Claims 1, 6, 11 and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant introduces the expression, "said infection is caused by an infectious agent having a ***lipid bilayer".*** There is no support for this expression in the specification as originally filed and therefore deemed to be new matter. Instant specification does not teach what agents have a lipid bilayer.

2. Claims 1, 6, 11 and 38-41are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro inhibition of HSV and HIV by octylglycerol containing liposomes, does not reasonably provide enablement for generic 'a fatty acid monoglyceride of the formula in claim 1 and prevention of enveloped viral infection . The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with a method of prevention of an infection using a liposomal formulation containing a fatty acid monoglyceride of the formula in claim 1.

2) The state of the prior art: the state of the prior art is very high in terms of formulating the liposomal compositions containing specific drugs for the treatment of various diseases but not preventing disease with a generic term, infection which can be due to any microorganism.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: while there is general predictability in formulating the liposomal or proliposomal formulations, there is unpredictability in the art

of preventing disease states such as AIDS, HSV infections and other viral diseases. Infections can be caused by any organism including, viruses, bacteria, micobacteria, fungi and parasites. Just because one specific compound (octyl glycerol) inhibits a specific virus in vitro, one cannot extrapolate the results to prevention of the infection by that specific virus in vivo by any other single chain lipid, let alone prevent any infection caused by any other infectious agent. Recent well-known example of drug resistant strain of tuberculosis can be cited as interest. Furthermore, in vitro studies may or may not be enough to predict a compound's effect in vivo and the examiner cites the reference of Zips (In Vivo, 19, pp. 1-8, 2005) in this context (see page 1 (Translational research chain in evaluation of anticancer agents on col. 2, page 1 and page 3, col. 2, last but one para).

5) The breadth of the claims: instant claim is very broad in terms of the active agent and the viral diseases to be prevented. Said claim 1 does not recite any specific active agent and the specific viral disease to be prevented. There are several enveloped viruses and it is well known in the art that there are no specific drugs which can be effectively used against these viruses let alone prevent the diseases caused by these viruses.

6) The amount of direction of guidance provided: instant specification provides no guidance at all in terms of preventing disease states.

7) The presence or absence of working examples: as pointed out above, infection can be caused by any microorganism and instant specification provides no working examples as to how the diseases can be prevented using the claimed formulation. What

is shown in the examples is the use of one specific compound, 'octylglycerol' on specific viruses HSV and HIV in vitro.

8) The quantity of experimentation necessary: since the claim 1 does not recite any specific active agent and prevention of any specific disease state, it is difficult for one of ordinary skill in the art to choose the proper active agent and prevent a disease without undue experimentation.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that the claims are drawn to preventing only viral infections with a liposomal composition comprising a fatty acid monoglyceride of the claimed formula and therefore, the amended claim set is no longer subject to the above rejection. Applicant disagrees with the examiner's analysis of the lack of predictability when using an effective drug on a novel target and argue that evidence of such predictability can again be found in the use of TNF- alpha blockers in the treatment of various diseases sharing a common feature and as in the use of TNF-alpha blockers which target over-induced inflammatory responses, the instant invention also exploits a common feature shared by the viruses, namely that are all enveloped viruses. Applicant further gives drug resistant tuberculosis strain as evidence. With regard to the amount of guidance provided and the presence of working examples applicant argues that the specification provides examples of liposomal formulations that are effective in killing gonococcus, HSV-1, HSV-2 and HIV in examples 1 and 2 and that the specification provides an example of administration of a liposomal formulation in Example 3. According to applicant the demonstration of the in vitro efficacy of a representative species, octylglycerol, for use

on a number of representative enveloped viruses HSV-1, HSV-2 and HIV is more than sufficient as enabling working examples. Further according to applicant, given the scope of the amended claims, the presence of working examples, and the detailed description of the claimed formulations in the specification, the quantity of experimentation necessary to practice the full scope of the invention as claimes (d) is insignificant.

These arguments are not persuasive. What is shown in the specification is the in vitro effectiveness of octylglycerol against the three viruses. Based on these studies applicant drafts the claims drawn to prevention of enveloped viral diseases using fatty acid monoglycerides. First of all, just because they are effective in vitro in killing these viruses, one cannot extrapolate the results to prevention of these viral infections. Applicant is advised to note Ex parte Balzarini 21 USPQ2d, 1892 at page 1897 (Bd. PAT. App. and Int. 1991): We do not presume to tell appellants what evidence would be acceptable in rebuttal of these rejections. While we are not requiring human clinical trials, it may well be that in 1987 or even now those skilled in this art would not accept anything short of such human clinical trials. There is no evidence of record that experimental animal models have been developed in this area which would have been predictive of human efficacy. The examiner also cites references which show the ineffectiveness of the microbicidal, nonoxynol-9 in prevention of HIV infections, though this compound was shown to be an effective barrier to HIV in laboratory studies (Public Health Agency of Canada, April 2003; The Bay Area Reporter, November, 2000) and the ineffectiveness of Carraguard, one of the highly developed candidates in this field which failed to prevent HIV transmission in a Phase III trial (Bioactive Polymers, 6-9-08).

Furthermore, instant claims are drawn to topical formulations, oral formulations, nasal formulations, ophthalmic formulations and even parenteral formulations. Instant specification does not teach adequately how the prevention of viral diseases can be accomplished by just by application to the eye or other modes of administration claimed.

The rejection is maintained.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 6, 11 and 38-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to b) in claim 1, the compound is a ***fatty acid*** monoglyceride. However, in the formula there is no carbonyl group contributed by the fatty acid carboxyl group. R1 and R2 are alkyl groups according to the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 6, 11 and 38-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Isaacs (5,466,714).

Isaacs discloses prophylaxis of enveloped viruses such as HIV using fatty acid monoglycerides which include octylglycerol (abstract, col. 8, line 41 through col. 11, line 15; col. 13, line 35 through col. 15, line 15; col. 19, line 30 through col. 20, line 65; col. 22, lines 30-36 and claim 1).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 6, 11 and 38-41are rejected under 35 U.S.C. 102(e) as being anticipated by Thormar (6,596,763).

Thormar discloses fatty acid monoglycerides for the prevention and treatment of enveloped viruses. The viruses include HIV and HSV and administration includes topical mode (col. 3, line 30 through col. 4, lines 52; col. 5, line 31 through col. 9, line 67; Examples and claims).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 6, 11, 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eibl (US 2002/0173489) in combination with Ho (US 2004/0208921, Hostetler (US 2001/0033862), Firshein (6,121,245) individually or in combination.

Eibl discloses formulations containing single chain lipids, which include alkylglycerols for viral infections such as HIV (0028, 0049-0057, 0064-0066, 0089, claims, claims 21, 26, 49, 51, 52, 54 and 57). What is lacking in Eibl is the teaching of the use of liposomes as carriers for the alkylglycerols.

Ho while disclosing liposomal formulations containing drugs for targeted delivery to lymphoid tissues teaches the advantages of liposomes or lipid complexes. According to Ho, as drug delivery systems, liposomes are especially promising because they can modulate the pharmacokinetics of liposome-associated drugs, which is not possible with non-lipid associated, or free drugs. Any number or combinations of lipid-anti HIV drug or lipid-anti-HIV biological complexes can be subcutaneously injected into HIV infected mammalian subject so that high concentrations of stable lipid-drug complexes can be preferentially delivered to the lymphoid tissue via lymphatic vessels, instead of delivering intravenously and HIV reservoirs within the infected lymphoid cells can be targeted effectively (abstract, 0004, 0009, 0013-0015, 0028, 0031, 0033, 0035, examples and claims). One of the lipids, which could be used, in addition in the liposomes is monoglycerides (alkylglycerols) (0034).

Hostetler while disclosing a method of treating viral infections teaches that in the form of liposomes, the antiviral agents are preferentially taken up by macrophages and monocytes, cells which have been found to harbor the target HIV virus (abstract, 0014, 0050 and 0051).

Firshein teaches while disclosing a method of treating cancer using alkylglycerols teaches that these compounds that these compounds can be incorporated into liposomes and that ordinary glycerol ethers, after incorporation into phospholipids, can activated the body's immune defense system (col. 4, lines 55-61; col. 10, lines 4-20).

It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for alkylglycerols taught by Eibl because of the advantages of liposomes taught by Ho, Hostetler and Firshein.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that none of the cited references teach or suggest prevention of the enveloped viruses. This argument is not persuasive since applicant bases the presumed prophylactic effect of the monoglycerides on their observed virucidal activity against enveloped viruses and Eibl shows the effectiveness the same compounds. Therefore, it would have been obvious to one of ordinary skill in the art that when applied topically, these compounds would effectively kill the viruses and prevent them from entering the host.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is

(571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK